Impact of Cold Ischemia Time on Frequency of Airway Complications Among Lung Transplant Recipients

Mirosław Nęcki[a], Remigiusz Antończyk[a,b], Anastazja Pandel[a,b,*], Martyna Gawęda[a,b], Magdalena Latos[a,b], Maciej Urlik[a], Tomasz Stącel[a], Marta Wajda-Pokrontka[a,b], Fryderyk Zawadzki[a,b], Piotr Przybyłowski[a,c], Marian Zembala[a,b], and Marek Ochman[a,b]

[a]Silesian Center for Heart Diseases, Zabrze, Poland; [b]Department of Cardiac, Vascular, and Endovascular Surgery and Transplantology, Medical University of Silesia in Katowice, Silesian Centre for Heart Diseases, Zabrze, Poland; and [c]First Chair of General Surgery, Jagiellonian University, Medical College, Kraków, Poland

ABSTRACT

Background. The cold ischemia time (CIT) is a period of time between harvesting an organ for transplant and its reperfusion just after implantation. CIT may have an impact on frequency of complications after lung transplant that can be treated by means of bronchoscopic intervention. The aim of the study was to investigate the correlation between CIT and frequency of bronchoscopic intervention.

Methods. The retrospective study consists of 91 patients: 22 single lung recipients (24%) and 69 double lung recipients (76%) who underwent lung transplant from March 2012 to June 2019. All statistical analyses were performed in SPSS 25.0 and R 3.5.3. The *P* levels less than .05 were deemed statistically significant.

Results. The average CIT in single lung transplant was 5.91 hours, and in double lung transplant it was 8.61 hours. For the 4- to 8-hour CIT the percentages were 80.95% for single lung recipients and 46.38% for double lung recipients. For CIT longer than 8 hours, the following percentages were observed: 9.53% in single lung transplant and 53.62% in double lung transplant. Each subsequent hour of CIT exponentially increases the risk of intervention 1505 times (50.05%).

Conclusions. Prolonged CIT seems to be a risk factor for airway complication, especially in the double lung recipient group.

LUNG transplant (LTx) remains the only therapeutic option for patients with end-stage lung diseases [1]. Despite enormous progress in the selection of donors and recipients and improvement both in surgical techniques and postoperative patient management, LTx is still associated with a relatively high risk of complications (2%-32%) [2–6]. Some of the most significant problems are airway complications (ACs), which include airway stenosis, dehiscence of the bronchial anastomoses, and various forms of impaired healing (excess of necrotic tissue or hypertrophic granulation). The main factors that are considered to have an impact on occurrence of ACs include cold ischemia time (CIT), length of the donor bronchi, surgical technique, use of mechanical ventilation, immunosuppressive agents, postoperative infections, and more [7–9]. Nevertheless, because of the lack of a widespread scale for respiratory complications after LTx, the assessment of their frequency performed by different LTx facilities produces various results, making the research set on evaluating its impact very difficult.

Therefore, there are still doubts because of the lack of conclusive data whether the length o CIT has a significant impact on the frequency of complications after transplant [10–15].

According to the Registry of the International Society for Heart and Lung Transplantation the median CIT in double

*Address correspondence to Anastazja Pandel, Silesian Centre for Heart Diseases, ul. Marii Skłodowskiej-Curie 9 Pawilon C, 41-800 Zabrze, Poland. E-mail: anasazja@hotmail.com

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lung transplant (DLT) was 5.5 hours, while single lung transplant (SLT) had a median CIT of 4.2 hours [10].

The aim of the study was to investigate the whether there is a correlation between CIT and the frequency of bronchoscopic intervention (BI).

MATERIALS AND METHODS

Patients

The study design was single-center retrospective cohort research. We analyzed data from 91 patients with available data who underwent LTx from April 2013 to June 2019 in Silesian Center for Heart Diseases (Zabrze, Poland). Median age at referral for LTx was 41 years old (range, 15-65 years). Heart-lung transplant and retransplant recipients were excluded from the study. The number of DLTs was 69 (75.82%). Demographic and clinical features of the studied group with the division into SLT and DLT groups are presented in Table 1.

Airway Complications

This article describes interventions required in case of any airway stenosis (at the bronchial anastomosis or lower, eg, bronchus intermedius), granulation, or the presence of necrotic tissue. No patients presented with any type of anastomotic dehiscence; therefore, such complication is not taken under consideration in this study.

Surgical Technique

Bronchial anastomoses were performed after excision of native lung and preparing the donor lung with absorbable sutures. Membranous part was sewn with continuous suture of pds 4-0, and pds 3-0 single sutures were used 1 per cartilage.

Organ Preservation

All of the lungs were flushed with extracellular, low-potassium, dextran-based electrolyte preservation solution in accordance to procurement protocol.

Cold Ischemia Time

CIT was defined as the time between aortic cross-clamp performed during organ procurement surgery and lung allograft reperfusion during LTx surgery. For DLTs the reperfusion of the second lung defined the duration of CIT.

Statistical Analysis

All statistical analyses were performed in SPSS 25.0 (IBM, Armonk, NY, United States) and R 3.5.3. The *P* levels less than .05 were deemed statistically significant. For analyses involving number of BIs, tests adequate for Poisson distribution were used since our data consisted of counts in a given period of time. Specifically, uni- and multivariate Poisson regression were used as well as Poisson test. Interaction effect of variables in multivariate Poisson regression was assessed with partial response plot. For dichotomous discrete variables (occurrence or lack of intervention) multivariate logistic regression analysis was performed.

For the analysis of demographic and clinical features of the studied group Student *t* test was used.

Table 1. Demographic Features of the Studied Group

Variables	SLT (n = 22)	DLT (n = 69)	*P* Value
Recipient Related			
Age, mean (SD), y	46.91 (12.81)	35.97 (14.27)	.002
Female sex, No. (%)	8 (36.36)	29 (42.03)	.638
Diagnosis, No. (%)			
CF	0 (0)	31 (44.93)	.004
COPD	10 (45.45)	16 (23.19)	
ILD	8 (36.36)	14 (20.29)	
IPAH	3 (13.64)	6 (8.7)	
Other	1 (4.55)	2 (2.9)	
BMI, mean (SD)	21.73 (3.64)	20.45 (3.79)	.169
GFR, mean (SD), mL/min/1.73m^2	97.49 (36.34)	133.18 (55.76)	.006
HGB, mean (SD), mmol/L	11.71 (2.67)	11.67 (3.11)	.963
RBC, mean (SD), millions/mL	5.21 (0.88)	5.03 (0.74)	.350
HCT, mean (SD)	44.3 (4.24)	42.68 (5.89)	.254
FEV_1, mean (SD), %	44.47 (27.41)	26.82 (15.44)	.030
FVC,%	60.1 (20.96)	43.1 (16.5)	.003
Donor Related			
Age, mean (SD), y	38.73 (13.35)	37.45 (12.5)	.682
Female sex, No. (%)	7 (31.82)	25 (38.46)	.576
BMI, mean (SD)	23.25 (2.56)	23.53 (2.8)	.671
Cause of Death, No. (%)			
Brain hemorrhage	11 (50)	36 (55.38)	.679
Head trauma	10 (45.45)	24 (36.92)	
Stroke	0 (0)	3 (4.62)	
Other	1 (4.55)	2 (3.08)	
Transplant Related, mean (SD)			
Waiting time, d	268.55 (347.77)	273.29 (282.97)	.949
CIT, h	5.91 (1.93)	8.61 (2.12)	< .001
1-y Follow-up			
GFR, mL/min/1.73m^2	46.65 (11.3)	58.82 (27.78)	.015
RBC, millions/mL	3.99 (0.52)	3.88 (0.52)	.476
HGB, mmol/L	7.34 (0.89	7.11 (0.89)	.395
HCT	0.35 (0.04)	0.35 (0.04)	.555
FEV_1, %	58.08 (16.44)	66.92 (25.09)	.234
FVC, %	72.08 (16.48)	76.02 (20.34)	.521
5-y Follow-up			
GFR, mL/min/1.73m^2	52.1 (13.26)	57.6 (32.32)	.703
RBC, millions/mL	4.38 (0.84)	4.69 (0.97)	.550
HGB, mmol/L	7.5 (1.16)	8.04 (1.27)	.432
HCT	0.37 (0.04)	0.39 (0.06)	.351
FEV_1, %	45.33 (16.17)	73.71 (32.55)	.079
FVC, %	65 (15.3)	82 (10.34)	.036

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CF, cystic fibrosis; CIT, cold ischemia time; COPD, chronic obstructive pulmonary disease; DLT, double lung transplant; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GFR, glomerular filtration rate; HCT, hematocrit; HGB, hemoglobin; ILD, interstitial lung disease; IPAH, idiopathic pulmonary artery hypertension; RBC, red blood cell; SLT, single lung transplant.

RESULTS

Described results are the effect of the analysis pertaining to 22 single lung recipients and 69 double lung recipients. The average CIT in SLT was 5.91 hours, and in DLT it was 8.61 hours. A total of 9.52% of single lung recipients and 0% of bilateral lung recipients had CIT less than 4 hours. For the

4- to 8-hour CIT, the percentages were 80.95% for single lung recipients and 46.38 for double lung recipients. When it comes to CIT longer than 8 hours, we can observe the following percentages: 9.53% in SLT and 53.62% in DLT.

In multivariate logistic regression analysis with CIT included, the statistical significance in Table 2 relates to Wald's statistics determining the need for performing an intervention. Statistically significant results encompassed CIT and body mass index. Each subsequent hour of CIT exponentially increases the risk of intervention 1505 times (50.05%). The aforementioned analysis assessed that lesser body mass index might increase need for BI. Nagelkerke's R^2 model was used to confirm that multivariate logistic regression analysis satisfactorily predicts the probability of having to perform interventions ($P = .246$).

With univariate logistic regression analysis the result of CIT is not statistically significant ($P = .283$; hazard ratio, 1.004; CI, 0.997-1.011).

The results of multivariate Poisson regression analysis are presented in Table 3. If the procedure was performed before 2018, the probability of performing an intervention increases 3.6 times. Each subsequent hour of CIT exponentially increases the risk of intervention by 15.7%. The increase in donor age by every year escalates the chance of intervention by 0.9%.

Figure 1 presents the impact of CIT and donor age on the number of interventions required for a patient. If the donor is young, we can observe a large association between the duration of CIT and the number of interventions. With donor age the impact of CIT duration decreases. At donor age of 52 years we can hardly observe the impact of CIT on the number of interventions.

DISCUSSION

Our study assessed that the number of interventions increases along with the duration of CIT. This observation was especially noted among recipients who received lungs from younger donors. Our study provided the results suggesting that lungs procured from older donors are more immune to ischemia. A similar issue was studied by Mendogni et al [13]. Their research determined that there is a significant association between ACs and CIT, as prolonged CIT seems to be a risk factor for late AC development. Similar surgical technique involving absorbable monofilament sutures is used in our center as well. Their study assessed the issue by univariate analysis, while the strength

Table 2. Multivariate Logistic Regression Analysis: Possibility of Need for Bronchoscopic Intervention

Parameter	Parameter Assessment	SE	χ^2	*P* Value	OR	95% CI Lower	95% CI Upper
Operation after 2018	1.281	0.1763	52.767	< .001	3.600	2.548	5.085
CIT, h	0.146	0.0387	14.276	< .001	1.157	1.073	1.249
Donor age, y	−0.009	0.0045	3.879	.049	0.991	0.982	1.000

Abbreviations: CIT, cold ischemia time; OR, odds ratio.

Table 3. Multivariate Poisson Regression Analysis: Impact on the Number of Interventions per Patient in the First Year After Liver Transplant

Parameter	Parameter Assessment	SE	χ^2	*P* Value	OR	95% CI Lower	95% CI Upper
Age, y	0.022	0.035	0.404	.525	1.023	0.955	1.095
Sex, female	0.184	0.647	0.081	.776	1.202	0.338	4.276
BMI	−0.275	0.132	4.332	.037	0.760	0.587	0.984
Diagnosis							
CF	0.471	1.024	0.738	.691			
COPD	0.903	1.056	0.212	.645	1.602	0.215	11.930
Other	−1.340	0.957	0.732	.392	2.467	0.312	19.530
Diabetes	0.001	0.001	1.962	.161	0.262	0.040	1.707
Time on waiting list > 365 d	0.409	0.193	0.793	.373	1.001	0.999	1.003
CIT			4.496	.034	1.505	1.031	2.195

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CIT, cold ischemia time; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

of our work is that it has proved that CIT is a valid risk factor of AC in a multivariate regression analysis. Less recent research published by Murthy et al does not prove the connection between CIT and AC [5]. Donor age is also believed to be a risk factor of death after LTx. However, our research determined that older lungs are more immune to the effects of ischemia because the number of the BIs rose significantly with increase of CIT among patients with lungs from younger donors, whereas the same effect was not observed among recipients with lungs procured from older donors. The article published by Mulvihill et al suggested that even though prolonged CIT does not influence the survival, donors older than 50 years can be a risk factor associated with worse survival after LTx [16]. However, there are studies that suggest that donor age and CIT do not influence the survival as independent factors. The study by Meyer et al also claims that those 2 combined demonstrated a significantly worse survival at 2 years. Such combination was also noted as significant by other articles [17]. Novick et al state that not only older donors may have unfavorable effect on survival. Their study also claims that very young donors also may have a negative impact. An interesting finding was reported among pediatric LTx recipients [18]. As it was published by Hayes et al, 4 to 6 hours of CIT was associated with favorable outcome, whereas CIT of more than 6 hours and less than 4 hours provided worse results [19]. A provided explanation was that patient characteristics (severity of condition) predispose transplant teams to select geographically closer donors to avoid longer CIT as risk factors of worse survival.

This issue requires further research because most transplant centers' goal is to have the shortest CIT possible.

CONCLUSIONS

CIT influences the number of ACs that require BI. The effect of CIT on the frequency of BI is particularly clear among recipients with lungs from young donors. In the

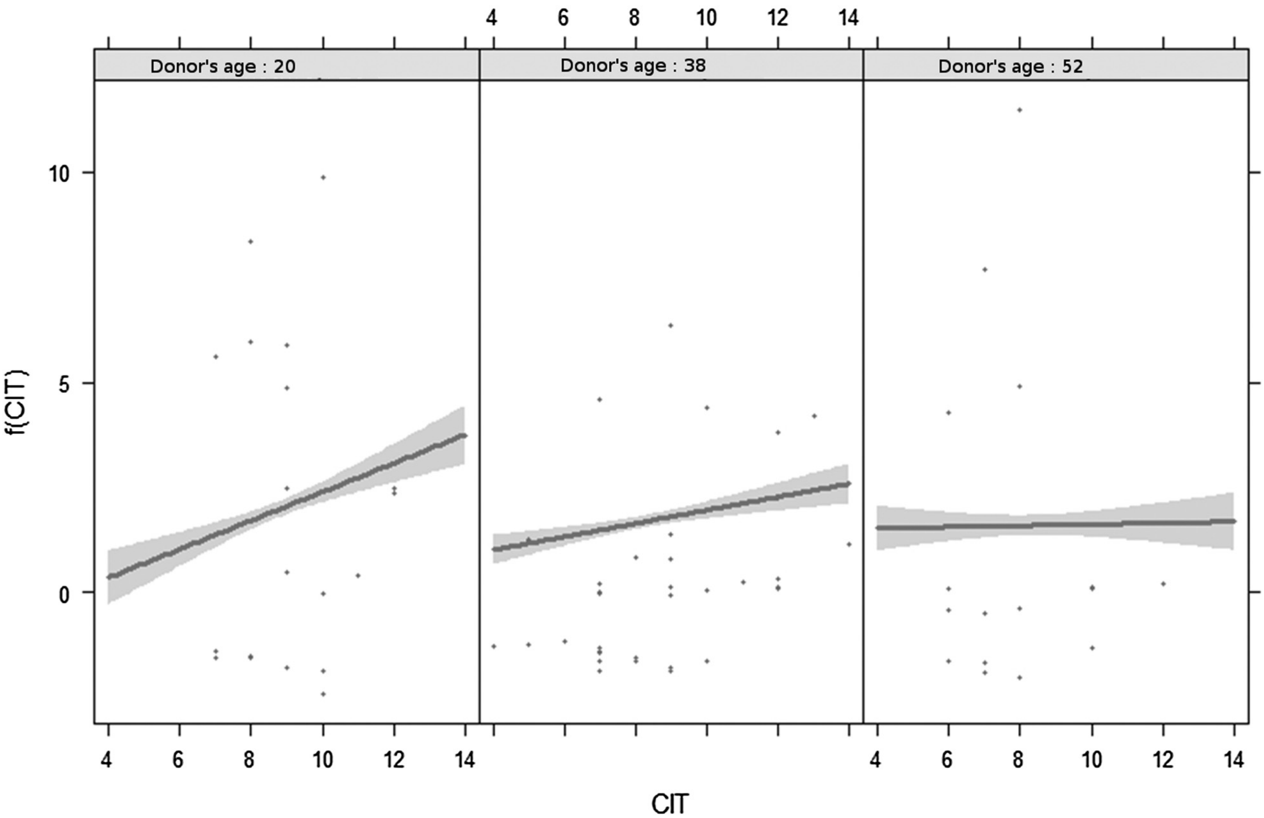

Fig 1. Edge effects graph describing the correlation between the number of interventions [f(CIT)] and the duration of CIT with different donor ages (20/38/52). CIT, cold ischemia time.

group of patients whose lungs were procured from older donors, the number of interventions was not as influenced by CIT. The study requires further investigations because authors are aware of its limitations.

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